REMARKS

Claims 39-43 are pending in this application. The present rejections to the claims are respectfully traversed.

Information Disclosure Statements

Applicants previously submitted two Information Disclosure Statements: one was filed on October 16, 2003 listing 30 references and a second Information Disclosure Statement was filed on December 12, 2003 listing 84 references.

Applicants note that in the Office Action dated January 21, 2004, the Examiner indicated that the Information Disclosure Statement submitted on October 16, 2003 was considered. Attached to that Office Action was only the first page of the PTO Form 1449 from the December 12, 2003 filing.

Applicants request that the Examiner provide complete signed off PTO forms for the Information Disclosure Statements filed on October 16, 2003 and on December 12, 2003.

Withdrawn Objections and/or Rejections

Applicants note with appreciation that the objection to claim 43 is withdrawn.

Applicants note with appreciation that the rejection of claims 39-43 under 35 U.S.C. § 102(b) as being anticipated by Wood et al., (WO99/14328) is withdrawn.

Applicants note with appreciation that the rejection under 35 U.S.C. § 102(b) as being anticipated by Valenzuela et al. is withdrawn.

Applicants note with appreciation that the rejection under 35 U.S.C. § 103(a) as being unpatentable over Valenzuela et al., in view of Ramakrishnan et al. is withdrawn.

Correction of Inventorship

Applicants note that the Examiner has indicated that the inventorship in this application has been changed. Applicants note that they have yet to receive a corrected filing receipt.

Rejections under 35 U.S.C. § 101 and 112, first paragraph

Claims 39-43 stand rejected under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by a substantial asserted utility.

Claims 39-43 stand rejected also under 35 U.S.C. § 112, first paragraph. Specifically since the claimed invention is allegedly not supported by either a credible, specific and substantial asserted utility or a well established utility, one skilled in the art would allegedly not know how to use the claimed invention.

Previously Applicant had provided section 1.132 declarations of Audrey Goddard and Avi Ashkenazi discussing the gene amplification assay.

The Patent Office indicates that the gene amplification assay does not establish a substantial utility for antibodies specific for the PRO269 polypeptides, to which this application is directed. The Patent Office agrees that the asserted utilities of cancer diagnostics and cancer therapeutics for the claimed proteins are credible and specific. However, the Patent Office asserts that the utilities are not substantial. Specifically, the literature allegedly evidences that gene amplification does not reliably correlate with increased mRNA or protein expression. Therefore, further research would allegedly be required to determine if the disclosed results regarding a gene amplification event in tumors is also reflected at the mRNA and protein levels. The gene amplification data are preliminary with respect to whether or not the claimed antibody can be used as a cancer diagnostic. Since the asserted utility that the claimed antibodies can be used as cancer diagnostics is allegedly not in currently available form, the asserted utility is allegedly not substantial.

For the reasons outlined below, Applicants respectfully disagree. With respect to claims 39 - 43, Applicants submit that not only has the Patent Office not established a *prima facie* case for lack of utility and enablement, but that the antibodies specific for the PRO269 polypeptides possess a credible, specific and substantial asserted utility and are fully enabled.

Applicants submit that there are numerous articles which show that generally, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. For example, Orntoft *et al.* (*Mol. and Cell. Proteomics*, 2002, Vol.1, pages 37-45, copy enclosed)

studied transcript levels of 5600 genes in malignant bladder cancers many of which were linked to the gain or loss of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (*Cancer Res.*, 2002, Vol. 62, pages 6240-45, copy enclosed) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (See page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.*, (*PNAS*, 2002, Vol. 99, pages 12963-12968, copy enclosed) who studied a series of primary human breast tumors and showed that "62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

Enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper

legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the majority of amplified genes, the teachings in the art, as exemplified by Ornoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis Declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO269 gene, that the PRO269 polypeptide is concomitantly overexpressed. Thus, Applicants submit that the PRO269 polypeptides and nucleic acids have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the protein for diagnosis of cancer.

Accordingly, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO269 polypeptide and for the antibody that specifically binds to PRO269. Further, based on this utility and the disclosure in the specification, one skilled in the art would know how to use the claimed antibodies at the time of filing.

CONCLUSION

It is submitted that the present application is in form for allowance, and such action is respectfully requested.

The Commissioner is authorized to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. 08-1641 (Docket No. 39780-1618 P2C34).

Respectfully submitted,

Date: November 3, 2004

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